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GENETIC BIOMARKERS IN PREDICTING SURGICAL OUTCOMES: A TRANSLATIONAL MEDICINE APPROACH

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ABSTRACT:
Subclinical acute rejection (SCAR) is a clinically relevant post-transplant complication and can have a negative impact on graft survival in the long-term, even in the absence of overt clinical signs. The need to detect molecular changes linked with SCAR early on is crucial in enhancing the prediction of post-surgical outcomes in kidney transplantation. This study aimed to identify candidate transcriptomic biomarkers associated with SCAR by comparing gene expression profiles between SCAR and histologically normal kidney transplant biopsy samples. A retrospective in silico transcriptomic analysis was performed using the GEO dataset GSE294632, comprising 24 renal biopsy samples (12 SCAR and 12 No SCAR) profiled on the Agilent SurePrint G3 Human Gene Expression v3 microarray platform. Differential expression analysis was conducted using the limma framework with empirical Bayes moderation, followed by gene annotation and integrative visualization, including volcano plots, principal component analysis, hierarchical clustering, and biomarker-specific boxplots. Although no genes met the adjusted false discovery rate threshold, exploratory analysis identified a coherent candidate gene signature associated with SCAR. Key biomarkers included POMT2, LAMA2, CSAD, RECK, HCG8, and lnc-IL32-1, reflecting a transcriptional pattern characterized by reduced expression of genes involved in extracellular matrix integrity and cellular maintenance, alongside increased expression of immune-related transcripts. These findings indicate that SCAR is associated with a biologically structured molecular signature capturing early graft injury processes. The results support the translational potential of transcriptomic biomarkers for improving post-transplant monitoring and predicting surgical outcomes.

KEYWORDS: kidney transplantation, subclinical acute rejection, transcriptomics, biomarkers, surgical outcomes

INTRODUCTION

The development of surgical science and perioperative care has changed the way of handling complex clinical conditions, and work is being more emphasized on enhancing the immediate and long-term outcomes. Modern surgery goes beyond the success of the procedure and considers the functional recovery and survival of the patient over time (Dean et al., 2019). Organ transplantation is one of the greatest advances in modern surgery, where it has provided a definite treatment to end-stage organ failure. After technical advances and advances in the postoperative management, the long-term graft survival is still a significant problem, with biological processes after transplantation still affecting the clinical results (Thongprayoon et al., 2020). Kidney transplantation is generally considered the best option in treating end-stage renal disease since it offers better survival and quality of life than dialysis. Nevertheless, patients who have transplants are still at risk of immune-mediated graft injury, which may jeopardize long-term results. Of special interest in this scenario is the phenomenon of subclinical acute rejection (SCAR), which is histological evidence of rejection without apparent clinical signs. This is an insidious mechanism that leads to progressive graft injury and has poor long-term outcomes when left undiagnosed (Van den Hoogen et al., 2021). It is thus possible to view SCAR as a serious post-surgical complication, which has a direct effect on graft survival, making it a crucial predictor of surgical outcome in transplantation.

The gold standard of renal biopsy diagnosis of rejection is the ability to examine graft pathology directly. Its invasive property and the risks that it entails restrict its usability in terms of repetitive monitoring and early detection (Schnuelle, 2023). Imaging can help with structural evaluation, but is not sensitive enough to detect early molecular alterations that occur before histological damage (Benjamens et al., 2020). Interest in molecular biomarkers of transplantation has been stimulated by the need to be able to measure non-invasively and early, diagnostic tools. Biomarkers give an insight into underlying biological processes and can even predict graft injury before clinical deterioration sets in (Novacescu et al., 2023). One such promising approach here has been transcriptomic profiling, which can be used to assess in detail the changes in gene expression with respect to immune activation and tissue damage. The subject of this study has already

been proven in past research that gene expression signatures may differentiate between subclinical and stable graft conditions, which may be used in diagnostics (Zhang et al., 2019). Molecular biomarkers that include blood have also been investigated to detect subclinical rejection, with researchers demonstrating the presence of clinically relevant gene signatures that can detect early immune activation (Friedewald et al., 2019). These results show the increasing importance of molecular diagnostics in enhancing transplant follow-ups.

The high-throughput technologies have increased the discovery of biomarkers using multi-omics technologies. These technologies allow complex biological systems to be analyzed in an integrative manner and help identify the regulatory networks in the development of diseases (Dar et al., 2023). Multi-omics platforms also augment the discovery of biomarkers through integrating information across multiple layers of biology, increasing the strength and interpretability of the results (Kumar et al., 2024; Raynaud et al., 2024). Recent discoveries of credible biomarkers are becoming more crucial in predicting the outcome of a disease and informing clinical decision-making. Prognostic biomarkers are vital in risk stratification of patients and personalized therapeutic interventions (Sah, 2025). Introduction of molecular biomarkers in clinical practice is one of the major steps towards precision medicine in transplantation. The changing treatment approaches in different fields of surgery further highlight the importance of biomarker-driven approaches to enhance long-term outcomes (Perdomo et al., 2023). Together, the above developments suggest that the transcriptomic biomarkers have the potential to be used in the process of detecting diseases as well as in predicting the post-surgical outcomes in transplant patients.

In spite of these advances, there is a paucity in translating transcriptomic results into clinically dependable biomarkers. There is frequently reported variability in reported gene signatures across studies, and reproducibility is of great concern. The variation in study design, cohort, and analytical approaches is one of the factors that lead to inconsistencies and restrain their use in clinical practice. There is no standardized and reproducible molecular signature of SCAR. The published transcriptomic data offer a chance to compare the pattern of gene expression on a large scale and to use the same analytical frameworks. Determining strong and biologically significant gene signatures in such datasets is critical in the development of biomarkers and enhancing their clinical applications.

The current research seeks to determine possible transcriptomic biomarkers that represent SCAR in kidney transplants by examining the differences in gene expression between SCAR and histologically normal samples. The study aims to define molecular signatures associated with post-transplant surgical outcomes through an organized computational methodology, and the aim is to add to the biomarker discovery in a translational medicine model.

2. METHODOLOGY

2.1 Research Design

This study utilized a retrospective, in silico transcriptomic study to examine the differences in gene expression in relation to SCAR in kidney transplant patients. A comparative two-group design was used, as SCAR samples were compared with histologically normal (No SCAR) controls. The analytical system was designed in a way that differentially expressed genes were identified, and candidate molecular biomarkers of divergent post-transplant surgical outcomes were obtained. This included data acquisition, preprocessing, normalization verification, statistical modelling, annotation, and integrative visualization, which is congruent with existing practices in microarray-based translational research.

2.2 Data Source

The information about gene expression was obtained in the Gene Expression Omnibus (GEO) database (accession number GSE294632) that represented a published study examining the molecular signatures of in kidney transplantation. The data involves transcriptomic data based on formalin-fixed paraffin-embedded (FFPE)-renal biopsy samples that were obtained in protocol-driven post-transplant surgical assessments. Histopathologic evaluation of samples was done to place them into the SCAR and No SCAR groups. The Agilent SurePrint G3 Human Gene Expression v3 microarray platform was used to profile the gene expression to provide a genome-wide measurement of transcript levels (Cox et al., 2026).

2.3 Data Preprocessing and Quality Assessment

Gene expression matrix and sample metadata were obtained with the processed series matrix file. The expression values were checked on the basis of distributional consistency between the samples. Summary statistics showed that the ranges, central tendencies and dispersion are similar, indicating that the data were already normalized properly at the source level and as such, they were not further transformed.

The curation of sample annotations was performed to obtain the variables of interest, including group classification (SCAR compared to No SCAR), sex, and tissue type. The resulting expression was compared with the resulting metadata to be able to map the expression profiles and phenotypic labels correctly. The samples that were under-annotated or had unclear identifiers were not found, and 24 samples were retained to be used in the downstream analysis.

2.4 Differential Expression Analysis

The limma (Linear Models of Microarray Data) framework was used to perform the analysis of differential gene expression. Each probe was fitted to a linear model to predict the differences in expression between the SCAR and No SCAR groups. The use of empirical Bayes moderation helped to stabilize the variance estimates and enhance statistical reliability in the case of small samples.

The first method of statistical significance was the Benjamini-Hochberg method to control the false discovery rate (FDR). Since none of the genes met the traditional cut-off of adjusted p-value < 0.05, an exploratory cut-off was used. The candidate differentially expressed genes were considered to be those genes with a nominal p-value less than 0.01 and an absolute log2 fold change of more than 1. This method is widely used in small-cohort transcriptomic analyses to put more emphasis on biologically meaningful signals and to take into consideration statistical limitations.

2.5 Probe Annotation and Gene Mapping

Platform-specific annotation data (GPL20844) were used to map microarray probe identifiers to gene symbols and gene names. Probes with valid and clear gene annotations were only kept for interpretation. Probes that did not have a gene symbol or did not map to a transcript were not sent to downstream analyses to facilitate biological relevance and interpretation. Where a number of probes were mapped to the same gene, probe-level results were kept as independent measures because of the exploratory nature of the study.

2.6 Exploratory Data Analysis and Visualization

Principal component analysis (PCA) was used to describe global transcriptional variation based on the normalized expression matrix. The method allowed visualization of the patterns of sample clustering and determining the components of variance that relate to group differences.

To simultaneously display the magnitude of a differential expression (log2 fold change) and statistical significance (p-value) of all genes, a volcano plot was plotted. The z-score standardized expression values were used to create a heatmap of the top-ranked differentially expressed genes. Both samples and genes were subjected to hierarchical clustering, showing the trends of co-expression and group-specific transcriptional signatures.

2.7 Candidate Biomarker Selection

The subset of top-ranked differentially expressed genes was chosen as candidate biomarkers on the basis of the statistical ranking as well as consistency of the patterns of gene expression across the samples. The criteria used to select them were high levels of fold-change, low nominal p-values, and explicit directional variation between the SCAR and No SCAR conditions. Gene annotations were only taken into account when validated.

Boxplot visualization was also used to determine the discriminative ability of the expression profiles of selected candidates across groups. Such genes were later characterized as the exploratory biomarkers of subclinical rejection and possible predictors of clinical outcomes following a transplant.

3. RESULTS

3.1 Dataset Characteristics

The transcriptomic data consisted of 24 kidney transplant recipients, each of the SCAR group and the histologically normal (No SCAR) group (Table 1). All the samples were taken on the basis of kidney tissue, and equal representation of males and females was maintained in both groups. Agilent SurePrint G3 Human Gene Expression microarray platform (61,142 probes) was used to perform gene expression profiling.

Table 1. Dataset summary and sample characteristics

Parameter	Value
Dataset ID	GSE294632
Platform	Agilent SurePrint G3 Human GE v3
Total samples	24
No SCAR samples	12
SCAR samples	12
No SCAR (Male)	7
No SCAR (Female)	5
SCAR (Male)	8
SCAR (Female)	4
Tissue type	Kidney
Total probes analyzed	61,142

3.2 Differential Gene Expression Analysis

The limma framework with moderation of empirical Bayes was used to conduct a comparison of differential expression between SCAR and No SCAR groups. There were no genes that reached the high threshold of false discovery rate (FDR < 0.05), but some genes exhibited high levels of nominal significance (P < 0.01) with significant fold changes. A volcano plot (Figure 1) is used to show the distribution of differentially expressed genes; it shows genes that were up-regulated and those that were down-regulated between the two conditions.

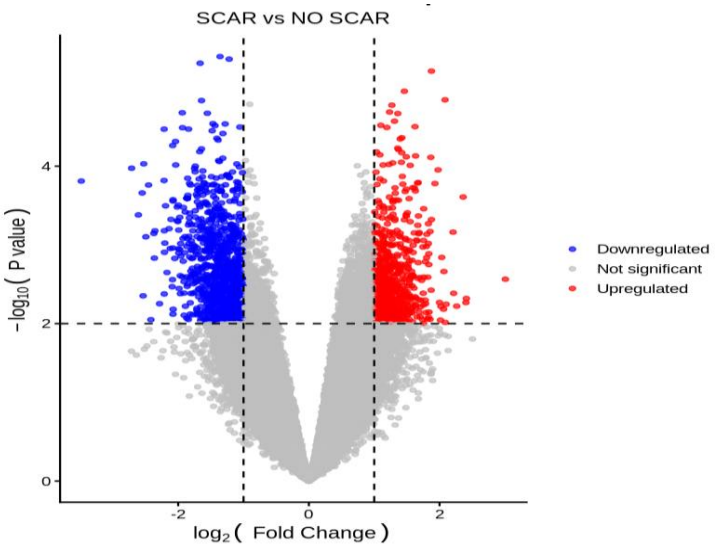

Figure 1. Volcano plot of differential gene expression between the SCAR and No SCAR groups

The volcano plot illustrates the separation of genes in terms of the magnitude of change in expression and statistical significance. A subset of genes exhibited substantial transcriptional changes (|log2FC| > 1), indicating biologically relevant variation associated with subclinical rejection.

3.3 Identification of Top Differentially Expressed Genes

In order to further describe the transcriptional landscape, nominal p-values and fold-change magnitude were used to identify the top differentially expressed genes (Table 2). These genes featured both protein-coding transcripts as well as long non-coding RNAs, as they represent a variety of biological processes.

Table 2. Top differentially expressed genes between the SCAR and No SCAR groups

Gene	Description	log2FC	Avg Expression	P value	Adj P value
POMT2	protein-O-mannosyltransferase 2	-1.36	7.82	4.1e-06	8.6e-02
LAMA2	laminin, alpha 2	-1.22	12.02	4.4e-06	8.6e-02
CSAD	cysteine sulfinic acid decarboxylase	-1.67	11.47	4.9e-06	8.6e-02
HCG8	HLA complex group 8	1.46	9.80	1.1e-05	8.6e-02
RECK	reversion-inducing-cysteine-rich protein with kazal motifs	-1.64	7.72	1.5e-05	8.6e-02
lnc-IL32-1	lnc-IL32-1:1	1.27	10.99	1.7e-05	8.6e-02
FOXD4	forkhead box D4	1.23	9.59	2.1e-05	8.6e-02
lnc-SLC23A1-1	lnc-SLC23A1-1:1	-1.94	7.57	2.1e-05	8.6e-02

These findings show that a number of genes related to the extracellular matrix organization, metabolic processes, and immune regulation have a different expression pattern in SCAR samples than in controls.

3.4 Global Expression Patterns and Sample Clustering

PCA and hierarchical clustering were conducted to evaluate the overall variation in transcriptomics. PCA showed clear separation of the SCAR and No SCAR samples based on the principal components, signifying the systematic variations in the gene expression profiles (Figure 2).

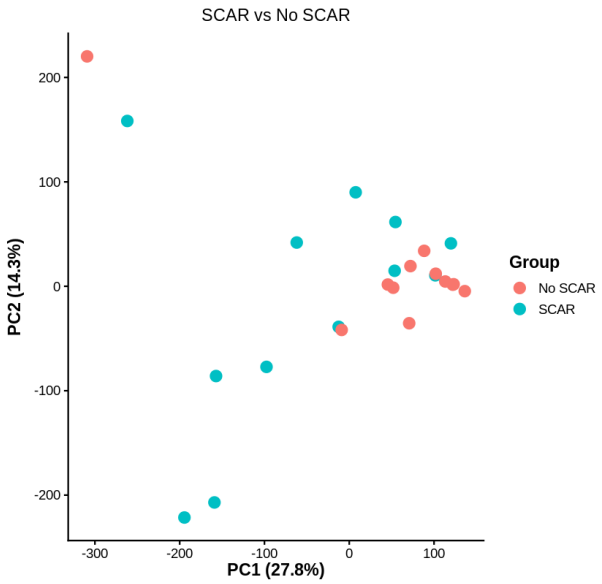

Figure 2. Principal component analysis of transcriptomic profiles

Moreover, the top differentially expressed genes were hierarchically clustered to show apparent segregation between the two groups, which in turn endorses the existence of stable transcriptional signatures related to subclinical rejection (Figure 3).

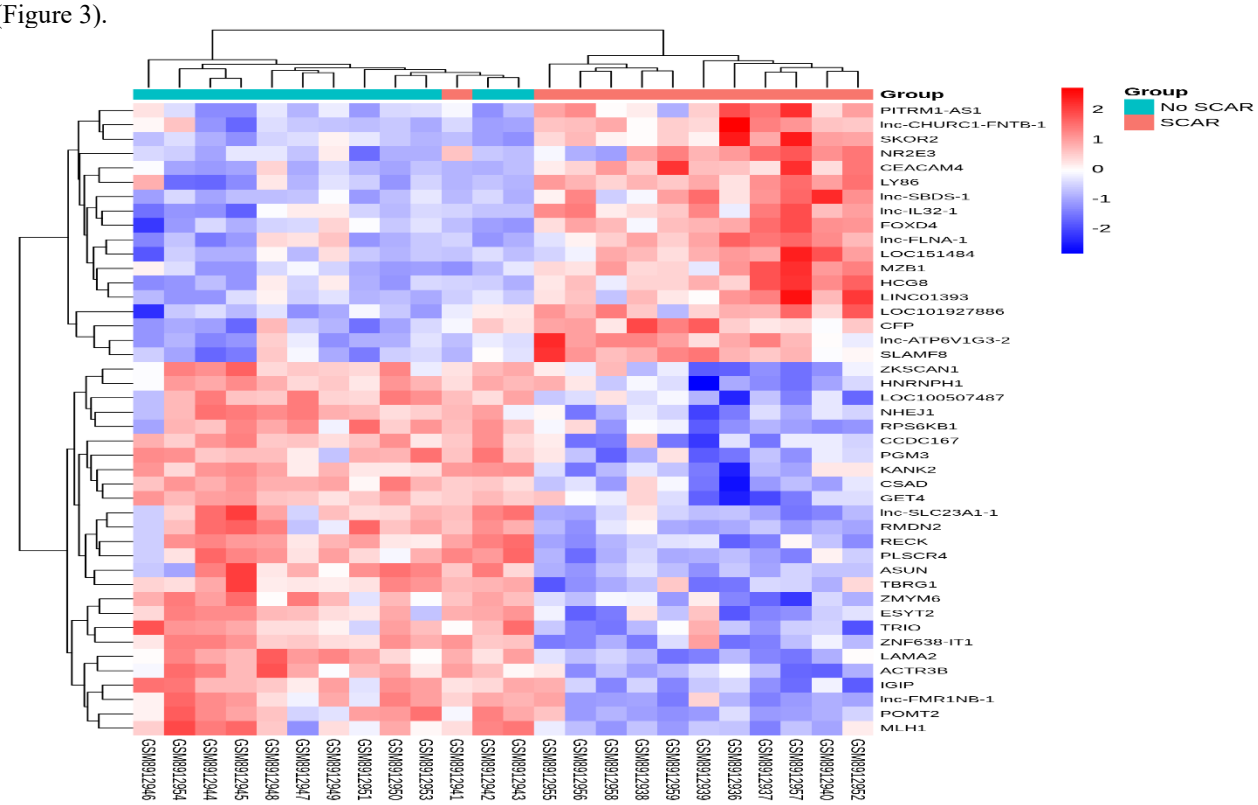

Figure 3. Heatmap of top differentially expressed genes

The heatmap also shows coordinated changes in the state of the gene clusters up or down, which may indicate some underlying biological pathways that have to be followed during disease progression.

3.5 Candidate Biomarker Identification

Differential expression analysis was used to select a subset of candidate biomarkers to further evaluate. These genes showed a balanced representation of the differences in expression between the SCAR and No SCAR groups and were plotted by boxplot analysis (Figure 4, Table 3).

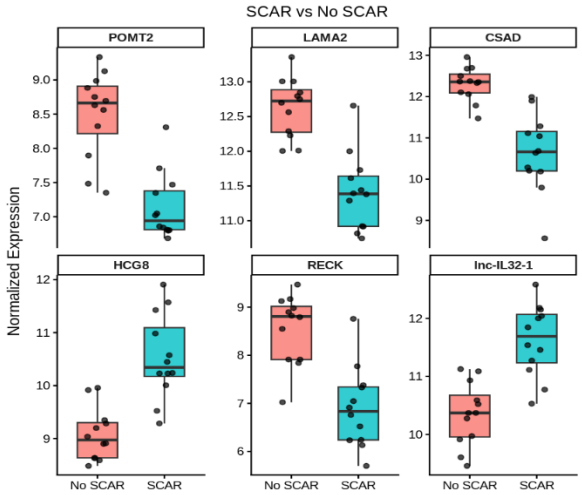

Figure 4. Boxplots of candidate biomarker expression across SCAR and No SCAR groups

Table 3. Candidate biomarker panel associated with SCAR

Gene	Description	Regulation (SCAR vs No SCAR)	log2FC	P value	Adj P value
POMT2	protein-O-mannosyltransferase 2	Downregulated in SCAR	-1.36	4.1e-06	8.6e-02
LAMA2	laminin, alpha 2	Downregulated in SCAR	-1.22	4.4e-06	8.6e-02
CSAD	cysteine sulfinic acid decarboxylase	Downregulated in SCAR	-1.67	4.9e-06	8.6e-02
HCG8	HLA complex group 8	Upregulated in SCAR	1.46	1.1e-05	8.6e-02
RECK	reversion-inducing-cysteine-rich protein with kazal motifs	Downregulated in SCAR	-1.64	1.5e-05	8.6e-02
lnc-IL32-1	lnc-IL32-1:1	Upregulated in SCAR	1.27	1.7e-05	8.6e-02

The distributions of these candidate biomarkers across groups also further validate their differential regulation and possible application in differentiating SCAR and stable transplant conditions.

The overall findings indicate a group of genes that regulate extracellular matrix, immune signalling, and metabolism, which can be considered potential biomarkers of SCAR.

4. DISCUSSION

The transcriptomic signatures of SCAR showed a consistent biological pattern but not a gene-level variation. Though no genes passed the most stringent false discovery threshold, the set of candidate genes that were identified using nominal significance and fold-change magnitude showed consistent separation between the SCAR and the histologically normal samples in various methods of analysis. This uniformity suggests that the transcriptional differences that are observed are biologically organized even with statistical constraints. A prevailing trend was observed, with less expression of the genes related to structural integrity and maintenance of cells and more expression of immune-related transcripts. Such a signature is an indication of early graft injury where the tissue architecture is impaired, but the immune activation is also triggered. Clinically, this type of molecular phenotype is an early manifestation of post-surgical graft dysfunction, and it occurs before clinical manifestations of such phenomena appear, but it already affects the long-term outcomes of transplantation.

The candidate biomarkers obtained in this research give a hint of the molecular mechanisms of post-surgical graft in kidney transplantation. The downregulation of POMT2 observed indicates the interference with the glycosylation processes of proteins that are fundamental in guaranteeing the structural integrity and stability of cells. Since the role of POMT2 is well-known in tissue development and integrity, a decrease in its expression can indicate the impaired cellular structure in the transplanted organ, which can become susceptible to structural damage after surgery (El-Dessouky et al., 2020). The same trend can be observed with LAMA2, which encodes a major extracellular matrix constituent that helps to preserve the integrity of basement membranes. A decrease in the expression of LAMA2 means that the extracellular matrix is not organized and such an activity is essential to maintaining tissue stability in transplanted organs. The observation of LAMA2 deficiency in correlation with impaired organ homeostasis supports the conclusion that its downregulation can be indicative of premature structural impairment affecting graft functioning (Pita, 2024). Functional studies also help prove that the loss of laminin-related signaling disrupts cellular functions and regeneration, which can be important in identifying long-term surgical outcomes in transplant environments (McGowan et al., 2025). This decrease in CSAD expression demonstrates a metabolic aspect of graft injury. CSAD plays a role in the production of taurine, and taurine deficiency has been linked to damaged allografts of the kidneys. Reduced CSAD levels could thus reflect metabolic stress levels and cellular adaptation impairments, both of which have been reported to play a role in graft dysfunction after transplantation (Rinaldi et al., 2024).

RECK downregulation implies maladjustment of the extracellular matrix remodeling. RECK is involved in regulating the degradation of the matrix and preserving the tissue architecture. It is less expressed and can facilitate the environment that allows pathological remodeling to occur, thus contributing to progressive structural damage, which negatively influences the outcomes of surgery in transplanted organs (Matsuzaki et al., 2024). Conversely, the HCG8 and lnc-IL32-1 upregulation is an indication of the activation of immune-related pathways. HCG8, which is found in the HLA region, is in line with alloimmune activation, which is a key mechanism of graft rejection. The heightened expression of lnc-IL32-1 is additional evidence of the existence of inflammatory signaling because IL-32-related pathways have been linked to the activation of immune cells in kidney tissue. This is consistent with the information that has been provided on the use of IL-32-positive immune and resident cells in the pathogenesis of inflammatory diseases of the kidney (Truglia et al., 2025). Collectively, these genes characterize a complex molecular signature of structural compromise, metabolic dysregulation and immune activation. This kind of integration is especially applicable to the scenario of transplantation, the outcome of which, in terms of surgical success, depends on the interaction of tissue integrity and immune tolerance. The differences in the definition of outcomes in clinical settings also highlight the necessity of molecular biomarkers to reflect underlying biology instead of just clinical outcomes (Lu et al., 2025).

The gene expression patterns we observed in this paper are in line with more general translational biomarker literature, in which complicated clinical phenotypes are generally related to complex molecular signatures and not the impact of individual genes. Biomarker discovery models based on omics lay stress on the significance of a multimodal approach in capturing disease-relevant mechanisms, which underlie the multi-gene profile here (Bravo-Merodio et al., 2019). Recent transcriptomic and proteomic investigations in kidney injury have also determined molecular signatures of maladaptive responses to tissue stress, especially those pathways associated with structural integrity and cellular adjustment. Such findings are similar to the current results as both structural and metabolic elements play a role in the observed transcriptional profile (Wen et al., 2023). Such molecular signatures have also been shown to have clinical implications, with research indicating that multiomics biomarker panels are more predictive of long-term graft outcomes than traditional clinical markers. That supports the possible value of the defined set of genes as a component of a more comprehensive prediction system of transplant success (Batko et al., 2025). Moreover, immune-related biomarkers were found to be associated with graft outcomes, indicating the relevance of inflammatory pathways in predicting transplant outcomes (Cherukuri et al., 2021). The presence of structural and remodeling-related genes is also in line with the findings of chronic kidney disease studies, where the same molecular events are associated with progressive organ dysfunction. This implies that the injury caused by transplants can have similar biological pathways to other causes of renal failure (Kobayashi et al., 2022).

The results indicate that transcriptomic biomarkers have the potential to measure early-onset molecular alterations relating to post-surgical graft outcomes. Simultaneous structural, metabolic, and immune-related signals integration gives a more complete picture of graft status compared to single parameters. This justifies that molecular profiling be used as an adjunctive method to the traditional diagnostics, and that they may find application in the early diagnosis, risk stratification, and personalized post-transplant care.

There are some restrictions that should be taken into consideration. The small sample size used relatively restricts statistical power and could be the reason why the genes did not satisfy the stringent multiple-testing thresholds. Only one dataset and microarray platform were analyzed, which could influence the generalizability. The identified biomarkers can be construed as candidates instead of validated predictors.

Future studies are warranted to confirm these results using larger independent cohorts and combine transcriptomic results with other layers of omics to enhance predictive ability. Longitudinal studies will also be critical towards establishing whether these molecular signatures are preceded by clinical or histologic changes, and thus, establishing their usefulness in predicting the post-surgical outcomes. These findings can also be more fully translated into clinical action tools by the development of multi-marker predictive models.

5. CONCLUSION

Transcriptomic analysis of kidney transplant biopsy samples revealed a consistent molecular signature of the SCAR, which is a low expression of genes related to structural integrity and cellular survival, and a high expression of immune-related transcripts. The candidate biomarker panel, comprised by POMT2 LAMA2, CSAD, RECK, HCG8 and lnc-IL32-1, indicates that outcomes of surgical procedures after transplant are influenced by the interaction of extracellular matrix disruption, metabolic stress and immune activation. These results also corroborate the usefulness of transcriptomic analysis as a translational method of identifying early graft-related biological changes that otherwise might not be evident when using conventional clinical evaluation. Another principle supported by the study is that it is possible to interpret clinically relevant post-surgical complications in terms of molecular signatures but not solely based on histological findings. Caution should also be exercised in the interpretation since only a small exploratory cohort and one microarray data was used to make the analysis. Nevertheless, the trends identified give a biologically feasible basis to be validated in the future. Greater multicenter investigations combining transcriptomic, proteomic and circulating biomarker data will be required to validate these candidates and will be used to establish their predictive value in post-transplant monitoring and personalized graft management.

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